REMARKS

Claims 27, 29-50 and 52 are pending in the present application. Claims 1-26, 28, and 51 have been canceled. Reconsideration of the application is respectfully requested in view of the following responsive remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

In the office action of March 14, 2008, the following actions were taken:

(1) Claims 27, 29, 31-50, and 52 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Cserhati and Hollo, *Intl. J. Pharmaceutics* (1994) 08:69-75 (hereinafter "Cserhati") in view of Links and Lewis, *Drugs* (1999) 57(3):293-308 (hereinafter "Links") and further in view of U.S. Patent No. 5,840,714 (hereinafter "Zmitek"); and

(2) Claims 27 and 30 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Cserhati in view of Links, Zmitek, and Baumann and Preiss, *J. Chromatography* (2001) 764:173-192 (hereinafter "Baumann").

It is respectfully submitted that the presently pending claims be examined and allowed. Applicants submit that each and every amendment herein, and throughout the prosecution of the present application is fully supported by the specification as originally filed, and that no new matter has been added.

Claim Amendments

Independent claim 27 has been amended to include the elements of claims 33, 38, and 42, which have been subsequently canceled. Additionally, claims 34, 39, and 43 have been amended to correct dependency issues arising from the cancellation of claims 33, 38, and 42. As such, no new matter has been presented.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 27, 29-50, and 52 under 35 U.S.C. 103(a) as being unpatentable over several references.

The Applicant does not deem it necessary to recite the entire case law standard required in order to establish a *prima facie* case of obviousness. However, the Applicant would like to briefly remind the Examiner of the required three criteria for a *prima facie* case of obviousness, namely 1) that the asserted references as modified or combined must teach or suggest each and every element of the claimed invention, 2) that the asserted references as modified or combined must provide a sufficient likelihood of successfully making the modification or combination, and 3) that the Examiner must identify a reason for the modification or combination asserted. The recent *KSR* Supreme Court case does not change this basic analysis.

With the above background in mind, Applicants submit that the cited references do not support a *prima facie* case for obviousness.

Cserhati in view of Links

Claims 27, 29, 31-50, and 52 were rejected under 35 U.S.C. § 103 as being unpatentable over Cserhati in view of Links and Zmitek.

The Cserhati, Links, and Zmitek references, when combined, do not teach or suggest all of the elements of independent claim 27. Cserhati discusses the interactions of taxol and other anticancer drugs, including cyclophosphamide, with hydroxypropyl-β-cyclodextrin (HPβCD) in forming complexes. The disclosure further reports that the capacity of drugs to form inclusion complexes with HPβCD differs considerably according to chemical structure. The findings of Cserhati include that "the solubility of taxol can be enhanced by HPβCD" as "the complex [is] more hydrophilic than the uncomplexed drug." See page 72 and Abstract, respectively. Cserhati reports that the intensity of interaction is reported to increase with increasing hydrophobicity of the drug. See Abstract. As such, one skilled in the art would conclude that HPβCD is more useful in increasing the hydrophilicity of hydrophobic drugs. However, oxazaphosphorines, in accordance with the present invention, are hydrophilic and even hygroscopic. For example, ifosfamide has a solubility in water of 100 mg/ml. As such, the teachings of Cserhati can be said to teach away from the present invention.

As the Applicant has raised the issue of teaching away, the Applicant would like to review the current case law regarding teaching away for the Examiner's convenience. The Court of Appeals for the Federal Circuit has clearly stated that "an applicant may rebut a prima facie

case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In re Petersen, 315 F.3d 1325, 1331 (Fed. Cir. 2003). The Court has also stated that "[w]e have noted elsewhere, as a 'useful general rule,' that references that teach away cannot serve to create a prima facie case of obviousness." (emphasis added) McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1354 (Fed. Cir. 2001). In identifying the appropriate standard for teaching away, the Court has further stated:

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be **discouraged from following the path set out in the reference**, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, **a reference will teach away if it suggests that the line of development** flowing from the reference's disclosure **is unlikely to be productive** of the result sought by the applicant." (emphasis added) In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

In the present case, a person of ordinary skill in the art would be discouraged from using HPβCD to increase the hydrophilicity of the present oxazaphosphorines since they are already hydrophilic. Additionally, a person of ordinary skill in the art would be discouraged from using HPβCD to stabilize a hydrophilic oxazaphosphorines since Cserhati teaches that hydrophobic forces are responsible for complex formation. See Abstract. Therefore, complexing these oxazaphosphorines with HPβCD would not be obvious to one skilled in the art based on Cserhati.

Additionally, the method disclosed in Cserhati is quite different that the present claimed method. Specifically, Cserhati teaches that the Cyclophosphamide and HPβCD comes in contact in aqueous methanol medium in preparing a solution for loading and for development of chromatogram, and on a TLC plate (i.e. in presence of active silica) impregnated in n-hexane – paraffin 95:5 v/v. See page 70, 1st col. "Experimental" section. However, the presently claimed invention is a composition prepared for intravenous use comprising aqueous solution of oxazaphosphorine antineoplastic, HPβCD, and mesna.

Furthermore, while mesna is taught in Links as a chemoprotectant, it is clear from this disclosure that mesna is administered separately from the drugs even though such administration can be begin prior to or concurrent with the administration of cyclophosphamide. See page 304, 1st col., 2nd ¶; 2nd col., 3rd ¶; page 305, 1st col., 1st ¶. To be clear, Links' discussion over pages

304 and 305 describe separate administrations of the drug and mesna. The two drugs are stored separately and administered separately, in accordance with the current state of the art. However, more importantly, Links also discloses that mesna must be administered beyond the administration of ifosfamide or cyclophosphamide. See page 304, 2nd col., 3rd ¶.

As such, the disclosure in Links not only fails to disclose the present compositions but actually teaches away from such compositions. Specifically, Links states that "it is necessary to continue treatment with mesna beyond the completion of administration of ifosfamide or cyclophosphamide." See page 304, 2nd col., 3rd ¶. Additionally, Link explicitly states that the half life of mesna is 1 hour, further teaching away from a single administration of mesna and ifosfamide. See page 304, 2nd col., "Administration of Schedules." Such disclosure teaches away from a combined ifosfamide/mesna composition since Links requires continuing administration of mesna after completion of the ifosfamide administration. As previously discussed, a reference that teaches away from the present invention cannot be used to establish a *prima facie* case of obviousness. Specifically, one of ordinary skill in the art would be discouraged from combining ifosfamide with mesna in a single composition since Links teaches a continuing administration of mesna after completion of the ifosfamide administration.

The Examiner has now cited Zmitek as teaching the use of complexing drugs with β-cyclodextrins to lower toxicity. See Office Action, page 3. Specifically, the Examiner has stated that Zmitek teaches that β-cyclodextrins lowers the toxicity of "piroxicam, ibuproxam and ibuprofen." See Id. However, a close inspection of Zmitek reveals that Zmitek actually teaches that individual compositions must be tested in order to determine the effects of toxicity. Specifically, Zmitek describes "an inclusion complex of nicardipine or of its salt with β-cyclodextrin" and concludes that "no difference in toxicity between nicardipine hydrochloride bound into a complex and free nicardipine hydrochloride can be noticed." See col. 3, lines 13-20. Therefore, at most, Zmitek can be said to teach that compounds complexed with β-cyclodextrins may lower toxicity. Additionally, as Zmitek is silent on the present oxazaphosphorine-containing compositions, Zmitek does not teach the element of β-cyclodextrins complexed to such compositions or that oxazaphosphorine-containing compositions have lower toxicity when complexed to β-cyclodextrins. Additionally, the Applicants submit that complex drug formation depends on the method of preparation. See e.g.

"Effect of Processing Variables on Dissolution and Solubility of Piroxicam: Hydroxypropyl- β-Cyclodextrin Inclusion Complexes" Indian J. Pharm. Sci., 2007, 69:2, pages 323-326 by Doijad RC, Kanakal MM, Manvi FV. As such, the Applicant submits that the present combination does not teach each and every element of the pending claim set.

Furthermore, the Applicant submits that there is no suggestion in any of the references for combining mesna in a stable solution with oxazaphosphorines and HPβCD. The difficulties involved in making a ready-to-administer formulation containing cyclophosphamide or ifosfamide along with mesna are known in the art and discussed in the Applicants' specification. Given the relative doses of mesna and cyclophosphamide or ifosfamide required for efficacy, the long-felt need of such formulations are clear, particularly when continuous administration of neoplastic drug is indicated.

Additionally, the Applicant would like to address the Examiner's optimization arguments. The Applicant submits that optimization starts after the "process that works" is known. The present process was not known, nor could one of ordinary skill in the art have been able to perform the present process based on the disclosures of the prior art. As such, the Applicant submits that it is not possible to optimize the present process without first having the process. The present invention is altogether a different process that that described in the art, as previously discussed. As such, the Applicant submits that mere optimization of the art could not lead one skilled in the art to arrive at the present invention.

The Applicant also wishes to note that the Examiner has not addressed the teaching away arguments presented in Applicant's previous responses and provided herein. The Applicant submits that the cited references actually teach away from the present invention; and therefore, any rejection based upon such references is improper. If the Examiner disagrees with the Applicant's arguments, including the teaching away arguments, or any case law cited herein, the Applicant respectfully requests that the Examiner provide a detailed explanation of his position or counter arguments such that the present issues are well defined for appeal.

In view of the above, Applicants assert that the cited references do not support a *prima facie* case for obviousness of claim 27 or any of the claims depending from it, and respectfully request that the Examiner withdraw the rejection.

Cserhati in view of Links, Zmitek, and Baumann

Claims 27 and 30 were also rejected under 35 U.S.C. § 103 as being unpatentable over Cserhati in view of Links, Zmitek, and Baumann. Baumann is cited as teaching ifosfamide and cyclophosphamide as commonly used oxazaphosphorines in chemotherapy. However, Baumann does not remedy the deficiency of Cserhati, Links, and Zmitek to teach or suggest a stable, parenterally administrable formulation containing both cyclophosphamide or ifosfamide and mesna. The Applicant renews the above arguments with respect to the present combination. As such, the Applicant asserts that the cited references do not support a *prima facie* case for obviousness of pending claims 27 or 30.

The Applicant respectfully asserts the Examiner has not satisfied the requirement for establishing a case of *prima facie* obviousness in any of the above rejections. Therefore, Applicant respectfully submits that the pending claims are allowable, and urges the Examiner to withdraw the rejections.

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CONCLUSION

In light of the above, Applicant respectfully submits that pending claims 27, 29-50 and 52 are in condition for allowance. Therefore, Applicant requests that the present rejections be withdrawn, and that the claims be allowed and passed to issue. If any impediment to the allowance of these claims remains after entry of this Amendment, the Examiner is encouraged to call Gary P. Oakeson at (801) 566-6633 so that such matters may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fee or to credit any overpayment in connection with this Amendment to Deposit Account No. 20-0100.

DATED this 16th day of June, 2008.

Respectfully submitted,

Gary P. Oakeson
Registration No. 44266

THORPE NORTH & WESTERN, LLP
Customer No. 20,551
P.O. Box 1219
Sandy, Utah 84091-1219
Telephone: (801) 566-6633